CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

MEDICAL REVIEW(S)

2/20/01

MEDICAL OFFICER REVIEW
Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21,232	**Application Type: NDA**
Sponsor: Swedish Orphan AB	**Proprietary Name: Orfadin™**
Investigator: Multiple (Not named)	**USAN Name: Nitisinone**
Category: New Drug Product	**Route of Administration: Oral**
	Dosage Form: 2, 5, 10 mg capsules
Reviewer: William A. Lubas MD-PhD	**Review Date: 2/6/2001**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments	
12/27/1999	12/28/1999	NDA Seq013	Original Submission Treatment of Hereditary Tyrosinemia 1 (HT-1)	Vols. 1.1-1.12
9/7/2000	9/12/2000	NDA Seq014	Response to Refuse to File	Vols. 5.1-5.2

RELATED APPLICATIONS (If applicable)

Document Date	Application Type		Comments
12/9/1994	IND ——	Seq000	Original Submission Vol. 1.1, Vol. 3.1

APPEARS THIS WAY
ON ORIGINAL

REVIEW SUMMARY:

Orfadin™ was shown to be effective as an adjunct to dietary restriction of tyrosine and phenylalanine for the treatment of hereditary tyrosinemia type 1 (HT-1). Treatment with Orfadin™ resulted in a decrease in the incidence of liver failure, liver transplantation, hepatocellular carcinoma (HCC), porphyric crises and rickets in patients with HT-1 compared to historical controls. However, cases of liver failure, HCC and porphyric crises continued to occur. Patients need to be monitored regularly for plasma nitisinone concentration, plasma and urine succinylacetone levels, urine 5-ALA level, and erythrocyte PBG-synthase activity, to monitor the efficacy of therapy. Patients receiving optimal therapy still need to be screened regularly for the potential development of HCC by measurement of plasma α-fetoprotein concentration and by liver imaging. Improved long-term survival was seen for patients with the acute form of the disease, who presented with the onset of symptoms at less than 6 months of age. With longer follow up it is possible that survival for patients with the ——— may also improve, but this has yet to be determined.

The pivotal Phase II-III clinical trial, submitted by the sponsor utilized primarily the —— formulation of Orfadin™ available from 1991-1998. In 1996 a new —— starch formulation was introduced and since Feb. 1998 this was the only available formulation of the drug. There was no difference seen in serum nitisinone levels or biochemical markers in patients dosed appropriately with either the —— or —— starch (to-be-marketed) formulations. Similarly, there was no difference in clinical outcome between the two formulations measured as incidence of liver failure, death, liver transplantation, or HCC in patients followed for at least two years on either study formulation.

Therapy with Orfadin™ was well tolerated. Most serious adverse events seen in these studies were likely due to the natural history of HT-1 and not a consequence of treatment with Orfadin™. 18% of the patients in the Phase II-II clinical study were withdrawn due to death or liver transplantation, but this was less than half the rate seen in historical controls. A small incidence (1-3%) of transient leucopenia and/or thrombocytopenia was seen that may be related to treatment with Orfadin™. However, no patients developed infections or bleeding as a result of these episodes. Some patients responded to lowering the dose of Orfadin™, while others had normalization of their blood cell indices without need for a change in the drug dose. Routine monitoring of blood cell indices is recommended during treatment with Orfadin™. The most common adverse events were eye disorders including conjunctivitis, blepharitis, keratitis, eye pain, photophobia and corneal opacity. There were a total of 31 events in 14 different patients (7%) in the Phase II-III clinical study. These are likely to be related to tyrosinemia induced by treatment with the drug rather than to the drug itself, which had been seen in preclinical trials. Patients with eye symptoms were followed with slit lamp exams and a more restricted diet was implemented to maintain tyrosine levels below 500 µmol/L. Most episodes resolved within one week. All other adverse events occurred at a incidence of < 2% and are unlikely to be related to Orfadin™ therapy.

In conclusion, the to-be-marketed —— starch formulation of Orfadin™ was shown to be safe and effective in the treatment of HT-1 and should be approved as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of this disorder.

OUTSTANDING ISSUES:

OPDRA does not recommend use of the proprietary name Orfadin™ because of potential confusion with approved proprietary names, namely Rifadin, Coumadin, Oraphen-PD and Cefadin.

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	X	**Approvable**	_____ **Not Approvable**

SIGNATURES: **Medical Reviewer:** /S/ **Date:**

Medical Team Leader: **Date:**

1 GENERAL INFORMATION

Contact person: Ronald G. Leonardi 858-586-0751
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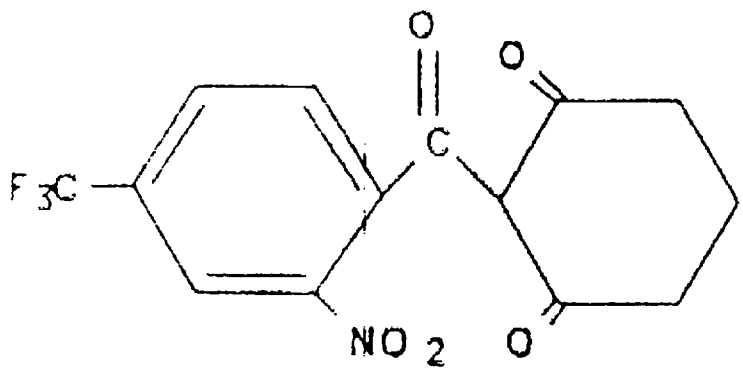
Drug Information

Generic name: Nitisinone
Proposed trade name: Orfadin™
Chemical name: NTBC
[2-(Nitro-4-triflouromethylbenzoyl)-1,3-Cyclohexane dione]

Chemical Structure:



Molecular formula: $C_{14}H_{10}F_3NO_5$
Molecular weight: 329.23

Proposed Indication: Treatment of Hereditary Tyrosinemia 1 (HT-1)

Proposed Dosage and Administration: 1-2mg/kg divided BID

Regulatory Background:

12/9/1994 Orginal submission of IND for NTBC-pharmacokinetic study to determine bioavailability, and kinetics of NTBC after oral administration

5/16/1995 Orphan Drug Drug Designation Letter

12/17/1998 pre-NDA meeting

7/7/1999 Fast Track Designation Letter

12/28/1999 NDA 21-232 CDER Stamp Date

2/25/2000 Refuse to File due to Biopharm Issues

5/16/2000 Meeting held with sponsor to address Refuse to File issues

9/12/2000 Sponsor resubmission of NDA

11/7/2000 NDA filed

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3 CHEMISTRY/MANUFACTURING CONTROLS

For a detailed analysis see Chemistry review. Orfadin™ is supplied in capsules containing 2 mg, 5 mg, and 10 mg of nitisinone, [2-(Nitro-4-triflouromethylbenzoyl)-1,3-Cyclohexane dione] with pregelatinised starch. The capsule shell is made up of gelatin and titanium dioxide and it is imprinted with iron oxide.

4 ANIMAL PHARMACOLOGY/TOXICOLOGY

For a detailed analysis see Pharmocology/Toxicology review.

Acute Toxicity: 20 Rats given 100 mg/kg orally survived, but 8/10 rats given 1000 mg/kg died. The oral lethal dose in rats and mice is estimated as around 500 mg/kg.

General Toxicity: The major toxicity observed in animal studies was corneal lesions seen in rats and dogs but not in mice, rabbits and monkeys. The lesions were seen at relatively low doses 0.1 mg/kg and were only partially reversible as ghost blood vessels remained. The lesions are believed to be due to increased tyrosine levels and not to the drug itself.

5 HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

For a detailed analysis see Pharmacology PK/PD review.

The terminal half-life of nitinsone was 54 hours in normal male volunteers. After a single dose of Orfadin™ the serum tyrosine level increased linearly until 48 hours after dosing, and remained constant at about 1200 ηmol/ml for at least 120 hours after testing. At 14 days after the initial dose the serum tyrosine level was still about 800 ηmol/ml. Fasted follow up samples taken a few weeks after the initial dose showed normalization of tyrosine levels.

6 HUMAN CLINICAL EXPERIENCE

6.1 Foreign Experience None.

6.2 Post-Marketing Experience None.

7 CLINICAL STUDIES

7.1 Introduction

The following clinical information on the use of Orfadin™ for the treatment of hereditary tyrosinemia type 1 was submitted in this NDA.

A single phase II-III study enrolling 207 patients treated with Orfadin™ by 96 investigators in 25 different countries from February 23, 1991 to August 21, 1997, dated 11/5/1999, and submitted 12/27/1999.

A Safety Update Report, dated 12/6/1999, including information on the original 207 patients and 75 new patients enrolled from August 22, 1997 to December 6, 1999.

A Safety Addendum Report, dated 12/6/1999, including information on 24 patients in 12 countries who received Orfadin™ for ———— without being enrolled in the multicenter clinical study.

A Safety Update Report, dated 9/12/2000, including information on the 238 patients already on Orfadin™ at the beginning of the safety update and 44 new patients enrolled from Jan.1, 1999 to Dec. 31, 1999.

A retrospective comparison of NTBC concentrations, laboratory data and Kaplan-Meier graphs between patients who received ———containing and patients who received starch containing NTBC formulations. Final Study Report 2000 010 02; August 14, 2000.

7.2 Proposed Indication

Orfadin™ is indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

7.3 Relevant Background and Rationale for Clinical Studies

- **Hereditary Tyrosinemia Type 1 (HT-1)**

Hereditary tyrosinemia type 1 is a rare autosomal recessive disorder with an estimated worldwide incidence of about 1 in 100,000 births. It occurs due to a deficiency in fumarylacetoacetase (FAH), the final enzyme in the tyrosine catabolic pathway (see APPENDIX). Heterozygotes are asymptomatic and have normal levels of tyrosine-related metabolites. The FAH gene maps to chromosome 15 q23-25, and 26 different single base substitutions have been identified. The identified mutations result in 16 amino acid replacements, 5 putative splicing defects, and 5 chain terminating nonsense codons. The mutations are spread over the entire gene with a particular clustering between amino acid residues 230-250.

This disorder can be characterized by liver failure, increased risk of hepatocellular carcinoma, coagulopathy, painful neurologic crises and renal tubular dysfunction resulting in rickets. The clinical course is variable which is partially due to the large number of possible mutations. Most patients, estimated at 77% in one study, present before 6 months of age with the acute form of the disease. These children exhibit symptoms of acute liver failure, recurrent bleeding and have a high risk of mortality within the first year of life. In the subacute form, children present with symptoms between 6-12 months of age and have a similar but less rapid progression of liver disease. In the chronic form symptoms do not appear until after one year of age. These patients have a still slower progression to liver failure. They also are at increased risk of developing hepatocellular carcinoma and progressive renal tubular dysfunction resulting in secondary hypophosphotemia and rickets. Patients with all forms of the disease are at risk of painful porphyria-like neurologic crises, which were seen in 42% of the patients in one study (Mitchell, G. et al). Dietary restriction of phenylalanine and tyrosine improves liver and kidney function but does not prevent the progression of the disease. Liver transplantation can correct most of the metabolic effects of the disorder except possibly

for the renal tubular dysfunction which may be due to the local production of toxic metabolites in the kidney.

- **Mechanism of Action of**

Orfadin™ has been developed for the treatment of HT-1 as a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway (see APPENDIX). By inhibiting the normal catabolism of tyrosine in patients with HT-1, it prevents the accumulation of the catabolic intermediates malelyacetoacetate and fumarylacetoacetate. These compounds are converted to succinylacetone and succinylacetoacetate, which appear to be responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate (ALA), which is a known neurotoxin and may trigger a porphyria-like crises.

Plasma tyrosine levels above 500 µmol/L can have toxic effects on the eyes (corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia), the skin (painful hyperkeratotic plaques on the soles and palms) and the central nervous system (variable degrees of mental retardation and developmental delay). Dietary restriction of phenyalanine and tyrosine in patients with HT-1 has been shown to limit the elevation of serum tyrosine levels and decrease the likelihood of toxicity. However, treatment of HT-1 with Orfadin™ results in elevated serum tyrosine levels. Patients treated with Orfadin™ need to be followed closely for the potential toxic effects associated with tyrosinemia.

7.4 Study Design

A Phase II-III nonrandomized, open label, noncomparative multicenter clinical study in 25 different countries, including the US, was performed to study the safety and efficacy of Orfadin™ as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of HT-1. For ethical reasons the study was open label and comparisons were made to historical controls treated with diet alone.

7.5 Protocol Overview

7.5.1 Inclusion Criteria

HT-1 verified by the presence of succinylacetone in the urine or plasma.

7.5.2 Exclusion Criteria

Prior liver transplantation.

7.5.3 Summary of Study Protocol

Formalized study instructions and report forms were distributed to the multiple centers enrolled in this study starting in March 1993. Regular visits were scheduled for patient histories and physicals, measurement of blood and urine samples, and imaging studies. Medical histories included information on drug dosage, dietary record and patient compliance. Blood samples were analyzed for succinylacetone, amino acids,

α–fetoprotein, erythrocyte porphobilinogen (PBG) synthase activity, electrolytes, liver function tests, coagulation profiles, and complete blood counts. Urine samples were analyzed for 5-aminolevulinate (5-ALA), succinylacetone, α–microglobulin, and amino acids. Imaging studies included chest X-rays, echocardiography, CAT scans, MRIs, and ultrasonograms.

Patients were started on a daily dose of 0.6-1 mg/kg/day. This higher dose gave better long term control of the biochemical parameters seen in HT-1, and resulted in a serum concentration of 20-39 μmol/L. Individual dosage readjustments were based on the biochemical response as estimated by measurements of serum and urine succinylacetone, urine 5-ALA and erythrocyte PBG synthase activity. After 1994, the serum concentration was also considered when making dosage changes.

The initial drug formulation consisted of capsules of Orfadin™ and [redacted] In November 1994 the drug manufacturing was transferred to Apoteket AB Production & Laboratories and capsules containing 2 to [redacted] mg of Orfadin™ with [redacted] were prepared. From 1996 to February 15, 1998 capsules containing 5, [redacted] and 10 mg of nitisinone mixed with [redacted] were formulated as well as a new 2 mg capsule containing [redacted] starch. From February 15, 1998 up to the present time the capsule formulation was changed to include only 2, 5, 10 mg of nitisinone mixed with [redacted] starch. The [redacted] starch was added [redacted] nitisinone in the capsules.

The median duration of treatment was 22.2 months with a minimum of 0.1 months and a maximum of 77.9 months. The entire clinical study covers a total of 441 patient years of treatment.

Reviewers' Comments:
The presently available to-be-marketed 5 and 10 mg formulations containing [redacted] starch were not available during the Phase II-III clinical study from 1991 to August 1997. Only the 2 mg capsule containing [redacted] starch was available from 1996 to the end of the study in August 1997. The data provided by the sponsor did not identify which if any of the patients in this study received the formulation containing [redacted] starch instead of [redacted] Since formulation changes can effect bioavailability of the drug components, it is not possible to link the efficacy and safety data presented using the trial formulation to the to-be-marketed formulation without a bioequivalence study. Therefore, the sponsor was asked to submit additional data comparing the two different formulations. See Efficacy of the To-Be-Marketed Formulation.

7.5.4 Defined Endpoints

Primary Endpoints:

- Long term survival
- Survival without need for liver transplantation
- Death or transplantation due to liver failure
- Development of hepatocellular carcinoma (HCC)
- Development of porphyric crisis

Secondary Endpoints:

- Effect on liver function- Serum ALT, AST, gamma-GT, bilirubin, albumin, prothrombin complex, serum α–fetoprotein
- Effect on kidney function- Urine α–microglobulin, amino acids; serum creatinine, serum phosphate
- Effect on hemic system- Complete Blood Count
- Effect on somatic development and clinical condition
- Effect on plasma amino acids including tyrosine
- Urinary excretion of phenolic acids

7.5.5 Statistical Considerations

- Kaplan-Meier analysis to evaluate survival data
- Logistic regression to evaluate the relationship between serum concentration and the reappearance of abnormal biochemical parameters
- Wilcoxon signed rank test to calculate p-values for biochemical parameters prior to treatment and after 1 year on Orfadin™.

Reviewers' Comments:
The study was open label and had no comparative control group for ethical reasons. The Kaplan-Meier survival analysis in this study therefore has to be compared to data from historical controls. Such comparisons can be misleading if the cohorts are different. The small number of patients in this study (207) and the variability in the clinical course of HT-1 increase the likelihood that confounding variables might preclude the usefulness of historical controls. For example, improved neonatal screening for patients with HT-1 and earlier dietary intervention could possibly slow the natural progression of the disease. In the historical study of Spronsen et al., patients who were identified by neonatal screening were excluded because dietary treatment was started before clinical symptoms had developed. Therefore, part of the observed increase in survival rate in this clinical study could be due to earlier dietary treatment in addition to the new drug therapy with Orfadin™.

The ability to correlate normalization of biochemical parameters with serum levels of Orfadin™ allows each patient to act as his own control and provides better evidence of drug efficacy.

7.6 Study Results

7.6.1 Patient Information

A total of 207 patients were enrolled in this study. The median age of patients at enrollment was 9 months with a range of 0 to 21.7 months

Table 1. Study Population Age and Gender Distribution			
	Number	%	Median treatment time (months)
Total population	207	100	22.2
Females	93	45	22.6
Males	114	55	21.1
Age 0-6 months at start	80	39	18.0
Age 6-24 months at start	62	30	20.4
Age > 24 months at start	65	31	27.7

7.6.2 Efficacy

7.6.2.1 Primary Endpoints

The primary endpoints were chosen to identify clinically important changes in morbidity and mortality in patients with HT-1. These included: overall long term survival, survival time without need for liver transplantation, incidence of progression to liver failure, incidence of hepatocellular carcinoma and incidence of porphyric-like crisis.

- **Long Term Survival:**

Table 2. Survival Probability of Patients with HT-1				
Study Population	Patients Treated with (95% confidence interval)		Historical Controls (Spronsen et al.)	
Survival Time	2yr	4yr	2yr	4yr
Age 0-2 months at start	88% (65: 100)	88% (52:100)	29%	29%
Age 0-6 months at start	94% (85: 100)	94% (80:100)	74%[1]	60%[1]
Age >6 months at start	97% (94:100)	93% (85:100)	96%	96%

[1] Data corresponded to patients 2-6 months of age at start of treatment.

Reviewer's comments
There is an obvious improvement in long term survival in this study, compared to historical controls, for patients diagnosed with HT-1 at less than 6 months of age. Patients diagnosed at less than 2 months of age showed the most dramatic improvement.

- **Survival Without Need for Liver Transplantation**

In this study 7 patients (3%) under went liver transplantation for liver failure. 7 patients (3%) were transplanted for hepatocellular carcinoma HCC. 6 patients (3%) were

transplanted for presumed HCC, which was not verified at time of transplant. In total, 20 patients (10%) were transplanted for liver failure or suspected HCC. An additional 7 patients (3%) were electively transplanted, for a total of 27 liver transplantations (13%) from all causes.

Reviewer's comments
There is a marked difference in the number of patients transplanted in this study ie. 13% compared to historical controls 25% (Spronsen et al.). In the prior study 7 patients (6%) were transplanted for end stage liver disease. 5 patients (5%) were transplanted for a combination of end stage liver disease and porphyria symptoms. 4 patients (4%) were transplanted for HCC. 6 patients (6%) were transplanted for presumed HCC which was not verified at time of transplant. An additional 4 patients (4%) were electively transplanted for a total of 26 liver transplantations (25%) from all causes.

- **Death or Transplantation Due to Liver Failure**

Death or liver transplantation due to liver failure during the course of this study occurred only in patients started on therapy before 24 months of age. The 4 year cumulative probability of death or transplantation due to liver failure was 13%.

Reviewer's comments
It is difficult to directly compare these data to historical controls. In the study of Spronsen et al., 32% of the patients died due to liver failure or recurrent bleeding and another 6% were transplanted due to liver failure over the course of that study. This suggests that treatment with Orfadin™ in this clinical trial markedly decreased the risk of death or transplant due to liver failure (38%, Spronsen et al. vs. 13% Orfadin™).

Comparing data for patients under 6 months of age, only 9% died or had a transplant due to liver failure in this study compared to 32% of the patients in the study of Spronsen et al. who died from liver failure or recurrent bleeding. This suggests that treatment with Orfadin™ reduces the risk of fatal liver disease in patients presenting at under 6 months of age with the acute form of the disease.

- **Development of hepatocellular carcinoma (HCC)**

Ten patients (5%) developed HCC. One each at 0.5, 4, 9, 10, 10, 12, 18, 30, 32, and 42 months after starting therapy with Orfadin™. Except for one patient that was 5 months old at the time of diagnosis, all patients were older than 1 year of age, with a mean age of 6 years and 2 months.

Reviewer's comments
There appears to be a relative decrease in the risk of developing HCC after therapy with Orfadin™ compared to dietery treatment alone (5% Orfadin™ vs. 8%, Spronsen et al. 1994) and (5% Orfadin™ vs. 11%, Mitchel G.A. et al. 1990). The overall risk is much lower than was seen in earlier studies prior to the initiation of dietary treatment (37%, Weinberg et al. 1976).

- **Development of porphyric crisis**

No cases of fatal porphyric crises were observed. Only one patient developed a porphyric crisis during the course of this Phase II-III study. The episode lasted 9 days and was characterized as mild in intensity. He had low serum nitisinone levels despite being on a relatively high drug dose of 1.5 mg/kg. Prior to the episode he had detectable urine and plasma succinylacetone, high urine excretion of 5-ALA and low PBG activity in erythrocytes. After increasing his dose to 3 mg/kg, plasma succinylacetone was still detectable, but urine succinylacetone and erythrocyte PBG activity were normal and 5-ALA was low.

Reviewer's comments
The risk of porphyric crises is markedly reduced by Orfadin™ treatment. Only one patient developed a crisis during this study and that was probably due to suboptimal therapy. In contrast, painful porphyric crises are a common neurologic manifestation of HT-1. In a series of 48 patients studied by Mitchell G. et al. 1990, 42% of the patients had crises. In the study of Spronsen et al. 10% of the patients died from consequences of porphyria-like crises.

7.6.2.2 Secondary Endpoints

The secondary endpoints that were monitored in this clinical study are laboratory values reflecting metabolic changes associated with the progression of the clinical course of HT-1 and changes in the clinical condition of the patients. The laboratory values, which were measured, include liver function tests, renal function tests, serum electrolytes, the platelet count, serum amino acids and urinary phenolic acids. The clinical condition of patients was assessed during histories and physical exams.

If left untreated HT-1 results in liver failure reflected in elevated liver function tests. Renal tubular dysfunction results in secondary hypophosphatemia and rickets. White blood cell and red blood cell indices do not appear to change but a mild decrease in the platelet count is observed. Serum tyrosine levels can become elevated if dietary restriction is inadequate. Urinary phenolic acids are typically within the normal range but can become elevated as a result of the inhibition of tyrosine catabolism by Orfadin™. The physical exam can show signs of liver failure (hepatosplenomegaly, abnormal bleeding, and ascites) and rickets.

- **LIVER FUNCTION TESTS**

Serum ALT- For most patients the serum ALT was in the reference range before the start of therapy (Reference value < 0.7), but the median serum ALT increased by 30% (p=0.007) after 1 year of treatment. This increase was noted as early as 1-month (0.72) and lasted until about 12 months after which the values normalized again.

Serum AST, γ–GT and bilirubin-In contrast serum AST, γ-GT and bilirubin were elevated but in the normal range for most patients at the start of therapy. After one year of therapy the median values dropped to below pretreatment values.

Table 3.
Serum Liver Function Test Values at Pretreatment and at 1 Year Visit

LFTs	Pretreatment	1 year Visit	p-value
ALT (U/L)	56	73	0.007
AST (U/L)	90	77	0.047
γ-GT (U/L)	107	42	<0.001
Bilirubin (mg/dL)	0.6	0.5	0.048

Albumin-For most patients the serum albumin was within the normal reference range before the start of therapy and increased slightly after 1 year of therapy 3.7g/dl-> 4.2g/dl (p<0.001).

Prothrombin Complex Time-The average median prothrombin complex time assessed as the International Normalized Ration (INR) for all patients for which data were available (n=60) was elevated at the start of therapy at 1.675. After 1 month of therapy the average median value of INR (n=51) had normalized to 1.15 (Reference range 0.80-1.20). However, there were seven patients who did not normalize during therapy.

Serum α-fetoprotein-The average median pretreatment α-fetoprotein level was 471 (μg/L) for all patients. After 1 year of therapy the average median value for all patients was 3 (P<0.001). In eight of eleven patients, in whom the α-fetoprotein concentration increased suddenly despite adequate therapy, HCC was verified by histopathology.

- **KIDNEY FUNCTION-**

Urine α-microglobulin-The average median pretreatment urine α-microglobulin level for all patients for whom data were available was 4.7 (g/mol creatine). By 6 months of therapy the value had decreased to 2.0 (p<0.001).

Urine Amino Acids- Urinary excretion of amino acids was followed only in patients with elevated levels at pretreatment (n=13), and only until these values normalized. The median pretreament value of 7535 mmol/mol creatinine had normalized to 1372 by 1 year of therapy (Reference range < 2510 at >2y/o; <3310 at 1-2y/o; <5320 at <0.5y/o).

Serum Creatinine- The serum creatinine was within the normal range at pretreatment. No significant changes were seen during therapy.

Serum Phosphate-The average median serum phosphate was low (4.0 mg/dl) at pretreatment for all patients for whom data were available (n=128), but was within the normal range (5.4 mg/dl) after 1 month of therapy (n=102, $p<0.001$).

- **HEMIC SYSTEM-**

Complete Blood Count- The serum hemoglobin and neutrophil counts were within the normal range at pretreatment. No significant changes were seen during therapy. The median pretreatment platelet count was low at 133,000/µl (n=127) but normalized by 1 year of therapy to 228,000/µl (n=53, $p<0.001$).

- **SOMATIC DEVELOPMENT AND CLINICAL CONDITION**

The linear growth and weight of patients treated with Orfadin™ was normal for age. The clinical condition of most patients improved with treatment as shown in Table 4.

Table 4.
Clinical Condition of Patients at Pretreatment and at 1 Year Visit

Clinical Symptom	% of patients pretreatment	% of patients at 1 year visit	number of patients
good general condition	56	90	50
signs of bleeding	14	3	37
signs of rickets	26	5	39
hepatomegaly	80	51	41
splenomegaly	38	31	42
ascites	33	0	42

- **Serum Amino Acids**-The change in average median values for serum amino acids from pretreatment to the 1 year visit are shown in Table 5.

Table 5.
Serum Amino Acids at Pretreatment and at 1 Year Visit

Amino acid	Reference Value	Pretreatment		1 Year Visit		Relative Change
		n	median (µmol/l)	N	median (µmol/l)	%
Tyrosine	25-125	193	140	114	387	270
Valine	50-330	193	160	114	206	129
Phenylalanine	30-120	193	65	114	56	86
Methionine	10-50	193	43	114	22	51
Glycine	70-500	193	439	113	375	85
Alanine	150-600	192	550	114	491	89

The largest change occurred in serum median tyrosine levels which increased 2.7 fold compared to pretreatment levels. At the 1 year visit 16% of the patients had values less than 250 µmol/l and 10% had values higher than 600 µmol/l. Patients with serum tyrosine levels > 500 µmol/l are at increased risk of eye symptoms.

- **Urinary Excretion of Phenolic Acids**-The median urinary excretion of phenolic acids increased from 475 mmol/mol creatinine (n=182) to 1740 at the 1 year visit (n=107, p<0.001). Phenolic acids are nontoxic intermediates produced from the catabolism of tyrosine due to the inhibition of 4-hydroxyphenylpyruvate dioxygenase by nitisinone.

7.6.2.3 Efficacy of the To-Be-Marketed Drug Formulation

Orfadin™ capsules were manufactured containing either —— (1991-1998) or —— starch (1996-present) as the excipient. After Feb. 1998 only the 2, 5 and 10 mg capsules containing —— starch were available. The original clinical efficacy data submitted in this NDA, and presented above, was generated from 1991-1997 using primarily the —— formulation. These data contained insufficient information on the to-be-marketed —— starch formulation to evaluate its efficacy. Therefore, the sponsor was asked to submit additional data comparing the efficacy of the —— starch formulation to the —— formulation. The sponsor submitted the following information for evaluation: serum NTBC concentration, urine and plasma succinylacetone levels, erythrocyte PBG-synthase activity, urine 5-ALA, and pertinent medical history (including incidence of death, liver transplantation, liver cancer, and liver failure leading to death or liver transplantation). The following analyses of these data confirm the efficacy of the —— starch formulation for the treatment of HT-1.

- **Study Population:**

The sponsor identified 53 patients started on the —— formulation who had a known date at which they were switched to the —— starch formulation. For comparison the sponsor also identified 55 patients who received only the —— formulation from the start of treatment. The sponsor only presented biochemical marker data for patients treated for at least 12 months (29 starch, 17 ——) or 18months (16 starch, 10 —— .

- **Nitisinone Concentration**:

An "Intent-to-Treat" analysis was performed for patients <6 months of age and 6-24 months of age at the start of treatment. No difference was seen between serum nitisinone levels in patients dosed appropriately with the two different drug formulations and followed out to 12 or 18 months of treatment. There is no reason to suspect any change in these data with longer duration of treatment.

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- **Biochemical Markers:**

1. **Urine succinylacetone**- > 90% of all patients on both formulations normalized by 2 weeks (<1 mmol/mol creatinine). Two patients in the starch treatment group and one in the —— treatment group never had normal values during the first year of treatment. But all three of these patients had no values reported after 7 days of therapy.

2. **Plasma succinylacetone**- Plasma succinylacetone levels normalized more slowly than urine levels. By 6 months > 80% of patients in both groups had normal levels (<0.1 μmol/L). Seven patients in the starch treatment group and 15 in the —— treatment group never had normal values in the first year of treatment. But none of these 22 patients had values reported after 5 months of therapy.

3. **Erythrocyte PBG-synthase**- Approximately 90% of all patients on both formulations had normalized erythrocyte PBG-synthase activity by 1 month (>0.58 μkat/g Hgb). Four patients in the starch group never had normal values in the first year of treatment. But two of these patients had no values reported after 7 days of treatment, the other two had nearly normalized values of 0.57 at day 244 and 0.46 at day 307.

4. **Urine 5-ALA**- >90% of all patients on both formulations had normalized urine 5-ALA by 2 weeks (<23 mmol/mol creatinine). Three patients in the —— treatment group never had normal values in the first year of treatment. But 2 of these patients had no values reported after 8 days of treatment, the other patient had a value of 23 at day 349.

- **Survival Analysis:**

There was no difference in death and liver transplantation due to liver failure between the starch (96%-2yr survival) and —— (92%-2yr survival) treatment groups.

There were no cases of verified HCC in either the starch or —— treatment groups.

There was no difference in death due to all reasons between the starch (94%-2yr survival) and —— (98%-2yr survival) treatment groups.

Looking at death and liver transplantation due to all reasons there were more cases in the starch treatment group (7) than in the —— group (1) but it was not statistically significant using the Gehan-Wilcoxon test. Out of the seven cases in the starch treatment group, one child died of prematurity, two were elective transplants and two were transplants due to suspected HCC, which were not verified after the operation. Only two out of the seven cases, occured due to liver failure compared to the one case of liver failure, which was seen in the —— treated group.

7.6.2.4 Summary of Reviewer's Comments on Efficacy

1) There was improvement observed in all five primary endpoints in this study compared to historical controls. These included: overall long term survival, survival time without need for liver transplantation, incidence of progression to liver failure, incidence of hepatocellular carcinoma and incidence of porphyric-like crisis.

- Improved long term survival during the 4 year follow up in this study occurred only for patients with the acute form of HT-1, that is patients under 6 months of age at the onset of symptoms. It is possible that with longer follow up Orfadin™ may also improve long term survival in patients with the subacute and chronic forms of the disease. In the historical controls (Spronsen et al.) patients with subacute and chronic forms of HT-1 showed 96% survival for the first six years following the onset of symptoms, 80% survival at eight years, and 60% survival after nine years. Studies with Orfadin™ were initiated in 1991 but enrollment of patients from multiple centers into the phase III part of this study did not begin until 1993. Therefore, these clinical data do not include patients with the subacute and chronic forms of HT-1 treated for 8 years or longer, who might be expected to show improved long term survival compared to historical controls.
- The improvement in survival of patients with the acute form of the disease is reflected in the reduced risk of liver failure in these patients and the reduced number of transplants required for these patients due to liver disease.
- There appears to be fewer cases of HCC in all patients in this study (5%) compared to historical controls (8-11%) on dietary therapy alone. This modest improvement is also reflected in the modest decrease in liver transplantation of patients with biopsy confirmed HCC in this study (3%) compared to historical controls (4%).
- There is a marked improvement in the risk of developing porphyric crises in patients with all forms of HT-1 treated with Orfadin™ in this study. There was only one patient who developed symptoms of porphyria in this Phase II-III study in contrast to historical controls (Mitchell G. et al., 42%). This is a significant improvement in the treatment of HT-1 because of the severe morbidity, which had previously been associated with these events. In one study (Spronsen et al.) 10% of the fatalities were associated with porphyric crises.

2) There was improvement observed in most of the secondary endpoints in this study as well, although it is not possible to directly compare most of these data to historical controls.

- Liver function tests including median AST, γ-GT, bilirubin, albumin, prothrombin time, and serum α-fetoprotein improved for patients over the first year of therapy for which comparative data were available. Although the average laboratory values improved, there were still individual patients for whom some of these tests did not normalize. In some cases this was due to low Orfadin™ concentrations suggesting suboptimal therapy, but in other cases it was due to liver failure that did not respond to treatment.
- Kidney function, estimated by serum creatinine, serum phosphate, urine α-microglobulin and urinary excretion of amino acids improved for most patients for

whom data are available in this study. No new cases of rickets developed during the course of treatment with Orfadin™.

- There were no significant changes in the average red blood cell or white blood cell counts associated with treatment. There was a modest improvement in the average platelet counts from 133,000 to 228,000/μl ($p<0.001$) after one year of treatment. Individual patients however, did develop episodes of transient thrombocytopenia and/or neutropenia which may have been related to Orfadin™ therapy (see SAFETY, Other Adverse Events).
- Somatic development and clinical condition improved for most patients on therapy.
- The observed changes in serum amino acids and increase in urinary phenolic acids reflect the inhibition of tyrosine catabolism consistent with the proposed mechanism of action of nitisinone ie. inhibition of 4-hydroxyphenyl pyruvate.
- The assay of serum nitisinone was shown to be a useful means of predicting the recurrence of abnormal biochemical parameters in the treatment of HT-1. Routine follow up of serum nitisinone, urine and plasma succinylacetone levels, erythrocyte PBG synthase and urine 5-ALA is a useful means to optimize therapy.

3) There was no observed difference in efficacy between the ——— and starch formulations in either the primary or secondary endpoints, which were tested.

In summary, Orfadin™ improves all of the primary and most of the secondary endpoints evaluated in this Phase II/III study showing it to be an effective adjunct to the dietary restriction of tyrosine and phenylalanine for the treatment of HT-1.

7.6.3 SAFETY

7.6.3.1 NTBC (Phase II-III) CLINICAL STUDY FROM FEBRUARY 1991-AUGUST 1997

207 patients received Orfadin™ during this study for a median treatment time of 675 days and a total of 441 patient treatment years.

7.6.3.1.1 Serious Adverse Events

37 out of the 207 patients (18%) were withdrawn from this study due to death or transplantation.

Table 6. Summary of Patients Withdrawn from this Study

Number	Reason for Withdrawal	End Result	n=207 (%)	Spronsen et al. (%)*
14	Liver failure	death or transplant	13	38
6	Suspected HCC but not verified at surgery	Transplant	3	6
9	Verified HCC	death or transplant	3	4
7	Elective	Transplant	3	4
1	Multi-organ failure	death (this patient presented with coagulopathy and porphyria and died 13 days after starting therapy)	0.5	

*The Spronsen et al. study included 108 patients followed for up to 11 years. The total patients-years of follow up in the Spronsen et al. study is not known so it is not possible to directly compare the data to the 441 patient-years of follow up in this study.

The adverse events listed in Table 6 are likely to be due to HT-1 and not a consequence of treatment. The incidence of liver failure, suspected HCC not verified by surgery, HCC verified at surgery and elective transplantation were all lower than seen in historical controls.

One patient had a mild porphyric crisis lasting 9 days believed to be due to suboptimal therapy. He had low serum nitisinone levels and elevated serum and urine succinylacetone levels that responded to increasing the drug dosage.

Four patients had seizures while on therapy, which were judged by the sponsor to be unrelated to the study medication. Two were associated with a febrile illness and one was due to hypoglycemia that was eventually controlled with [redacted] and enzymes.

There were six cases of transient thrombocytopenia with a probable causal relationship to treatment with Orfadin™. Three of these cases were considered severe with minimum platelet counts of 30,000/µl, 29,000/µl and 12,000/µl. No patients had symptomatic bleeding as a result of the thrombocytopenia.

One patient developed a craniopharyngioma requiring surgery, which was unlikely to be related to treatment with Orfadin™.

One patient had a single cyanotic episode, which the sponsor stated was unlikely to be related to Orfadin™ treatment.

7.6.3.1.2 Other Adverse Events

- **Eye Symptoms**

The most common adverse events were eye disorders, including conjunctivitis, blepharitis, keratitis, eye pain, photophobia, and corneal opacity. There were a total of 31 events noted in 14 different patients. Most of the episodes were transient lasting less than one week. Four patients had prolonged episodes lasting 16, 61, 99 and 672 days. These adverse events are likely to be related to tyrosinemia induced by the treatment with Orfadin™ and not due to the drug itself. Corneal lesions have been observed in animal toxicology studies in rats and dogs. Similar eye symptoms have been seen in other forms of hereditary tyrosinemia.

- **Transient Thrombocytopenia and Leucopenia**

The incidence of transient thrombocytopenia, leucopenia or both was 3%, 3%, and 1.5% respectively. One patient, who developed both leucopenia and thrombocytopenia, improved after the dose of Orfadin™ was decreased from 2 to 1 mg/kg. Another patient, who developed thrombocytopenia, had Orfadin™ stopped for 2 weeks but the platelet count stayed low for 3 months and slowly returned to normal after 5 months. In all other patients it appears that values normalized gradually without documented change in Orfadin™ dose. No patients developed infections or bleeding as a result of the episodes of leucopenia and thrombocytopenia. These adverse events are possibly related to treatment with Orfadin™.

- **Other Events**

All other adverse events occurred with an incidence of <2% and were unlikely to be related to Orfadin™ therapy.

Table 7. Adverse events with an unknown causal relationship to Orfadin™ treatment occurring in < 2% of the patients

Body System	Adverse Event	n	%
Cardiovascular	cyanosis	1	0.5
	headache	1	0.5
	hyperkinesia	1	0.5
	seizure	3	1
Fluid & Electrolytes	dehydration	1	0.5
	hypoglycemia	1	0.5
	thirst	1	0.5
Gastrointestinal	diarrhea	1	0.5
	enanthema	1	0.5

Table 7. Adverse events with an unknown causal relationship to Orfadin™ treatment occurring in < 2% of the patients			
Body System	Adverse Event	n	%
	gastritis	1	0.5
	gastroenteritis	1	0.5
	GI bleed	1	0.5
Infectious Disease	Bronchitis	1	0.5
	Otitis Media	1	0.5
	Infection	1	0.5
Hematological	epistaxis	2	1
Musculoskeletal	pathological fracture	1	0.5
Neoplasm	brain	1	0.5
Psychiatric	nervousness	1	0.5
	somnolence	1	0.5
Reproductive	amenorrhea	1	0.5
Skin, Hair & Teeth	maculopapular rash	1	0.5
	dry skin	1	0.5
	alopecia	1	0.5
	tooth discoloration	1	0.5
Vision	cataract	1	0.5

7.6.3.1.3 Overdose Exposure

Orfadin™ doses as high as 3 mg/kg/day were given in this study even though the recommended dose is 1-2 mg/kg/day. The highest serum nitisinone level reported in this study was 158 µmol/l. No adverse events were reported to be associated with high nitisinone levels in this study.

7.6.3.2 SAFETY UPDATE REPORT FROM AUG. 1997-DEC. 1999

A total of 187 patients were already on Orfadin™ at the beginning of August 1997 and 75 new patients were enrolled into the study from Aug. 1997-Dec. 1999. A Safety Update Report, covering this time period and dated Dec. 6, 1999 was submitted along with the original NTBC study. This data corresponds to an additional 290 patient treatment years.

7.6.3.2.1 Serious Adverse Events

There were 22 serious adverse events that were reported during this Safety Update Report (SUR) dated Dec. 6, 1999 (See Table 8).

Table 8. Summary of Patients with Serious Adverse Events in SUR

Number of patients with adverse events (# of pts)	Adverse Event or Reason for Withdrawal	Outcome	NTBC Study (n=207) 441 patient-years (# of pts/pt-yrs)	SUR (n=262) 290 patient-years (# of pts/pt-yrs)
11	liver failure or GI bleed	death or transplant	3.2	3.8
1	suspected HCC but not verified at surgery	transplant	1.4	0.3(↓)
1	verified HCC	transplant	2.0	0.3 (↓)
5	elective	transplant	1.6	1.7
1	multi-organ failure	death (patient was on therapy for 1 month before being identified as not having HT-1)	0.5	0.4
1	meningitis	death		0.4
1	septicemia	death		0.4
1	unknown febrile illness	death		0.4

There were 3 deaths in this safety update report due to infectious causes that are unlikely to be related to Orfadin™ therapy, one from meningitis, one from septicemia, one from an unknown febrile illness. One patient died from multi-organ failure after being on therapy for one month after presumably being misdiagnosed with hereditary tyrosinemia type 1.

The other 18 serious adverse events are likely to be due to HT-1 and not to the consequence of Orfadin™ therapy. These include 7 additional deaths, 6 from liver failure, and one from a GI bleed. The incidence of these adverse events is similar to what had been seen during the original NTBC Study Report. However, there is a trend toward

fewer transplants for suspected HCC and a lower incidence of HCC in this Safety Update Report.

7.6.3.2.2 Other Adverse Events

Table 9. Summary of Patients with Other Adverse Events in SUR

		NTBC Study Report		Safety Update Report	
	Adverse Event	# of pts	#of pts /(pt-yrs)	# of pts	# of pts /(pt-yrs)
Blood Disorders	Thrombocytopenia	6	1.4	2	0.7
	Neutropenia	2	0.5	2	0.7
	Leucopenia	4	0.9	0	0
Eye Disorders	Blepharitis	2	0.5	0	0
	Conjunctivitis	4	0.9	1	0.3
	Corneal Opacity	4	0.9	4	1.4
	Eye Pain	3	0.7	2	0.7
	Keratitis	5	1.1	3	1.0
	Photophobia	4	0.9	1	0.3

The most common adverse events in the SUR are similar to what had been previously reported in the NTBC Study Report.

All other Adverse Events occurred with an incidence of less than 2% and were unlikely to be related to Orfadin™ therapy.

7.6.3.3 SAFETY ADDENDUM REPORT

There were 24 patients treated with Orfadin™ for ——————who were not included in the NTBC Clinical Study.

7.6.3.3.1 Serious Adverse Events

There were 5 serious adverse events reported during this Safety Addendum Report that resulted in death or transplantation.

Table 10. Summary of Patients with Serious Adverse Events in the Safety Addendum Report

# of pts	Adverse Event or Reason for Withdrawal	End Result	First Study (n=207) 441 pt-years (# of pts /pt-yrs)	SAR (n=24) 13 patient-years (# of pts /pt-yrs)
1	liver failure or GI bleed or encephalopathy	death or transplant	3.2	7.7
1	verified HCC	transplant	2.0	7.7
1	elective	transplant	1.6	7.7

Table 10. Summary of Patients with Serious Adverse Events in the Safety Addendum Report				
# of pts	Adverse Event or Reason for Withdrawal	End Result	First Study (n=207) 441 pt-years (# of pts /pt-yrs)	SAR (n=24) 13 patient-years (# of pts /pt-yrs)
1	Unknown cause	death (no details provided)		7.7
1	respiratory insufficiency	death (treated for only 2 days)		7.7

This incidence of adverse events appears to be higher than observed in the NTBC Study Report. The small number of patients involved in this report makes it more difficult to accurately compare data to the original study. The trend toward a higher incidence of adverse events in this group suggests that these patients are receiving inferior care compared to patients enrolled in the NTBC study.

7.6.3.3.2 Other Adverse Events

There were no other adverse events reported in the Safety Addendum Report.

7.6.3.4 SAFETY UPDATE REPORT FROM JAN. 1-DEC. 31, 1999

A total of 237 patients were already on Orfadin™ at the beginning of this Safety Update. 44 new patients were enrolled during this treatment period. These data corresponds to an additional 254 patient treatment years.

7.6.3.4.1 Significant Adverse Events

There are 19 serious adverse reported during this Safety Update including 17 that are likely to be due to HT-1 and not a consequence of Orfadin™ therapy. In addition one patient had a case of retinal degeneration and one patient died from unknown causes. Out of the 17 adverse events that are likely to be due to HT-1, there were 5 cases of liver failure (5 deaths), 2 cases of porphyria (one death), 2 cases of cirrhosis and 8 cases of liver transplantation (2 for verified HCC). In general the incidence of these adverse events is similar to what had been seen during the original NTBC Study and earlier Safety Update Reports. Data in this safety update confirm that there continues to be a small incidence of liver failure, liver neoplasm and porphyria despite appropriate therapy.

Table 11. Summary of Patients with Serious Adverse Events in SUR

# of pts	Adverse Event or Reason for Withdrawal	Outcome	NTBC Study (n=207) 441 pt-years (# of pts/pt-yrs)	SUR (n=262) 290 pt-years (# of pts /pt-yrs)	SUR (n=281) 254 pt-years (# of pts /pt-yrs)
5	Liver failure or GI bleed	death or transplant	3.2	3.8	2.0
2	Suspected HCC but not verified at surgery	transplant	1.4	0.3	0.8
2	Verified HCC	transplant	2.0	0.3	0.8
4	Elective	transplant	1.6	1.7	1.6
2	Porphyria	One death	0	0	0.8
2	Cirrhosis		0	0	0.8

7.6.3.4.2 Other Adverse Events

Table 12. Summary of Patients with Other Adverse Events in SUR

		NTBC Study Report		Safety Update Report 1		Safety Update Report 2	
		n	n/(pt-yrs) %	n	n/(pt-yrs) %	n	n/(pt-yrs) %
Blood Disorders	Thrombocytopenia	6	1.4	2	0.7	1	0.4
	Neutropenia	2	0.5	2	0.7	0	0
	Leucopenia	4	0.9	0	0	1	0.4
Eye Disorders	Blepharitis	2	0.5	0	0	0	0
	Conjunctivitis	4	0.9	1	0.3	1	0.4
	Corneal Opacity	4	0.9	4	1.4	2	0.7
	Eye Pain	3	0.7	2	0.7	2	0.7
	Keratitis	5	1.1	3	1.0	2	0.7
	Photophobia	4	0.9	1	0.3	1	0.4

The most common adverse events in this Safety Update are similar to what had been seen previously in the NTBC Study Report and the earlier Safety Update Report.

All other adverse events occurred with an incidence of less than 2% and were unlikely to be related to Orfadin™ therapy.

7.6.3.5 SUMMARY OF REVIEWER'S COMMENTS ON SAFETY

The total exposure to Orfadin™ from Feb. 23, 1991 to Dec. 31, 1999 corresponds to almost 1000 patient treatment years, which should provide an adequate safety base for monitoring of clinical adverse events.

- **Serious Adverse Events**

There were no Serious Adverse Events in the NTBC Study, Safety Update or Safety Addendum Reports that could be directly attributed to therapy.

Most of the Serious Adverse Events observed in these studies have been seen as part of the natural history of HT-1. They include death or transplantation due to liver failure, and suspected HCC. The incidence of these events appears to be lower in the NTBC Study and Safety Update Reports compared to historical controls (see Tables 6 and 11), although direct comparison is difficult since historical studies do not provide information on patients-years of treatment.

There does seem to be a trend toward fewer transplants due to HCC or suspected HCC in the SUR compared to the original NTBC Study. This suggests, that with longer treatment, there may be improved survival of patients treated with subacute and chronic forms of HT-1, which typically result in death or transplant due to HCC.

However, it needs to be emphasized that despite adequate therapy some patients still develop HCC, liver failure or porphyric crises. Regular follow up of serum α-fetoprotein and liver imaging should be integrated into the treatment protocol to screen for HCC (see **WARNINGS** under drug labeling).

- **Other Adverse Events**

The major adverse effects, which may causually be attributed to Orfadin™, are eye symptoms, thrombocytopenia and leucopenia.

The eye symptoms included conjunctivitis, blepharitis, keratitis, eye pain, photophobia and corneal opacity. They are believed to result from tyrosinemia induced by treatment with Orfadin™ and are not due to the drug itself. The incidence of eye symptoms was 5.0% and 3.8% (events/patient-years) in the NTBC Study and the SUR respectively. The sponsor recommends adherence to a tyrosine and phenylalanine restricted diet to maintain plasma tyrosine levels below 500 μmol/L in order to avoid the toxic effects to the eyes (see **WARNINGS** under drug labeling).

Transient thrombocytopenia and leucopenia occurred at ≤ 1.4% and ≤ 0.7% (events/patient-years) in the NTBC Study and the SUR, respectively. No patients developed infections or bleeding as a result of these episodes. The sponsor recommends regular monitoring of platelet and white blood cell counts to help identify these events (see **WARNINGS** under drug labeling).

- **Drug Interactions**

There was no information on drug interactions in the NTBC Study, Safety Update or Safety Addendum Reports.

- **Overdose and its Treatment**

There was no information on overdose in the NTBC Study, Safety Update or Safety Addendum Reports.

- **Drug Abuse or Misuse**

There was no information on drug abuse or misuse in the NTBC Study, Safety Update or Safety Addendum Reports.

- **Human Reproduction Data**

There was no experience with drug exposure during pregnancy or lactation in the NTBC Study, Safety Update or Safety Addendum Reports. There is no reason to suspect that this drug would have abuse or misuse potential.

7.6.4 CONCLUSIONS OF STUDY RESULTS

Orfadin™ improved all of the primary endpoints and most of the secondary endpoints evaluated in the NTBC Phase II/III Clinical Study for the treatment of HT-1.

There were no serious adverse effects seen in any of the studies presented that could be directly attributed to Orfadin™. Most of the observed serious adverse events appeared to be a result of the natural history of HT-1, and treatment with Orfadin™ lowered the risk of these serious adverse events relative to the data that is available from historical controls.

There were adverse events, which may possibly be attributed to treatment with Orfadin™. These include eye symptoms, thrombocytopenia and leucopenia. All of these adverse events appeared to resolve without permanent sequelae, as long as appropriate monitoring and follow-up were performed. No patients withdrew from these studies due to these safety concerns. These adverse events do not contribute a significant risk to patients with HT-1 relative to the benefit that is obtained from this medication.

In conclusion, Orfadin™ is a safe and effective adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of HT-1.

8 LABELING

The medical reviewers changes to the sponsor's proposed label are underlined and in colored text.

WITHHOLD 11 PAGE (S)

Draft

Labeling

9 REVIEW of FINANCIAL DISCLOSURE

a) Outcome payments
None
b) Proprietary interest
None
c) Equity interest
None
d) Significant payments of other sorts
None

The sponsor certified that none of the 114 investigators in the clinical trials participated in financial arrangements with the sponsor. Since this is such a rare disorder with 207 patients distributed over 25 different countries, it seems unlikely that any individual investigator could substantially alter the clinical results observed in these studies for financial gain.

10 RECOMMENDATIONS

The labeling recommendations were incorporated into section 8, LABELING.

Orfadin™ should be approved for the treatment of HT-1.
Recommendation code: AE

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11 SIGNATURE PAGE

Reviewed by:

/S/ (2/6/01)

William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEDP

cc: Original NDA (NDA Archive DMEDP)
HFD-510/Division File
HFD-510/Lubas/Orloff/Su Yang

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12 REFERENCES

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13 APPENDIX

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TY OSINE DEGRADATIC PATHWAY

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